



Sleep deprivation, oxidative stress and inflammation

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Abstract

Adequate sleep is essential for normal brain function, especially during early life developmental stages as postnatal brain maturation occurs during the critical period of childhood and adolescence. Therefore, sleep disturbance and/or deficit during this period can have detrimental consequences. Many epidemiological and clinical studies have linked early life sleep disturbance with occurrence of later life behavioral and cognitive impairments. Role of oxidative stress and inflammation has been implicated in sleep deprivation-related impairments. This review article presents a detailed description of the current state of the literature on the subject.



1. Introduction

It is well known that sleep, especially during early life, is essential for proper brain development and function (Orzel-Gryglewska, 2010). Consequently, sleep deprivation (SD) in children and adolescents has been associated with affective and behavioral difficulties (Astill, Van der Heijden, Van Ijzendoorn, & Van Someren, 2012; Dewald, Meijer, Oort, Kerkhof, & Bogels, 2010). Relevant to this, in a longitudinal study, SD in children, 2.5–6 years old, were found to be associated with hyperactivity and behavioral abnormalities (Touchette et al., 2009). Later onset of anxiety and depression has also been associated with early life sleep problems (Gregory et al., 2005). In fact, some longitudinal studies suggest that early life sleep problems are highly predictive of future affective and behavioral problems (Gessa, Pani, Fadda, & Fratta, 1995). The role of sleep in several neurodevelopmental processes including synaptogenesis, synaptic pruning, neuronal myelination, and neurogenesis has been proposed. Consequently, sleep loss has been implicated in disruption of synaptic integrity and neural circuits maturation (Frank, Issa, & Stryker, 2001; Lopez et al., 2008). Oxidative stress, inflammation, and glial dysfunction are suggested as an underlying mechanisms (Atrooz, Liu, Kochi, & Salim, 2019; Cirelli, 2006). Before a detailed description of relevant studies, basic literature related to sleep physiology must be discussed.



2. Sleep physiology

Sleep is a physiological state characterized by lack of response to environmental stimuli. In vertebrates, sleep is defined as a specific pattern of synchronized electrical activity of the cortical area of the brain. Sleep is typically evaluated by polysomnography (PSG), which involves simultaneous recording of brain's cortical activity using electroencephalogram (EEG), eye movement using electrooculogram (EOG), and skeletal muscles' activity using electromyogram (EMG). In humans and other mammals, sleep consists of two main phases: rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM sleep is characterized by high amplitude low frequency EEG waves known as slow wave sleep, decreased muscle tone, and slow eye movement. While REM sleep is characterized by low amplitude high frequency waves known as active sleep, muscle atonia, and rapid eye movement. In humans, NREM sleep is further divided into

three stages; N1, N2, and N3, each stage has a defined EEG waves. During sleep, these phases alternate in a highly regulated pattern forming sleep cycles (Stenberg & Porkka-Heiskanen, 1990). Sleep/wakefulness state is regulated by the interaction of two processes; the circadian system (process C) and the sleep homeostasis (process S) (Borbely, 1982a; 1982b). Process C is controlled by the suprachiasmatic nucleus (SCN) within the hypothalamus. The SCN serves as the neural pacemaker of circadian timing cycle. It is mainly synchronized to environmental light/dark cycle and projects signals that control proper timing of physiological functions including sleep/wakefulness cycle. The daily circadian rhythm is 24 h under normal light/dark cycles, with sleep onset and wakefulness onset occurring at same time every day. Sleep homeostasis or process S is regulated by the sleep pressure generated after a period of wakefulness, hence, the level of process S increases with extended wakefulness and decreases after sleep onset. There are two hypothesis for sleep pressure generation; one is accumulation of sleep promoting substances such as adenosine and nitric oxide, second is the need for restoration of energy resources (Abrahamson & Moore, 2006). The interaction of the sleep homeostasis and the circadian rhythm regulates the timing, the depth and the duration of sleep. In fact, the alignment between the two processes is essential for body metabolism and brain function. Furthermore, disruption in sleep/circadian rhythm is associated with many metabolic, psychiatric, and neurodegenerative diseases (Wulff, Gatti, Wettstein, & Foster, 2010).

The wakefulness state is coordinated by several defined nuclei in the pons and midbrain areas known as ascending reticular activating system (ARAS). These wakefulness promoting cells are; noradrenergic (NE) cells in locus coeruleus, serotonergic (5-HT) cells in raphe nuclei, cholinergic (ACh) cells in pedunculopontine tegmentum and latero-dorsal tegmentum, glutamatergic cells (Glu) in midbrain, and dopaminergic (DA) cells in substantia nigra and ventral tegmental area. Projections of these waking promoting cells activate thalamo-cortical, hypo-thalamo-cortical and basalo-cortical systems. In addition to ARAS, there are five other groups of cells that promote wakefulness these groups include; histaminergic cells of posterior hypothalamic area, the hypocretin/orexin cells in lateral hypothalamus, cholinergic cells in basal forebrain, neuropeptide Y(NPY) containing cells in suprachiasmatic nucleus, and glutamatergic neurons in ventro medial prefrontal cortex (vmPFC). Activation of these systems maintain wakefulness by activation of cortex, however, lesion of one specific wakefulness promoting group may not induce changes in amount of wakefulness,

suggesting that all these groups of brain regions together contribute in promotion and maintenance of wakefulness but none of them is absolutely necessary for generation of wakefulness. Understanding sleep initiation and maintenance has been a challenge for decades. Initiation of sleep is suggested to be a result of successive passive and active physiological processes which leads to blockage of cortical sensory gates (Datta, 2010). The passive process that contributes to sleep initiation results from accumulation of neuronal activity-dependent metabolites. During wakefulness, metabolic products such as adenosine, nitric oxide, cytokines, and prostaglandins accumulate leading to slow down of wakefulness-prompting neuronal activity, which ultimately slows down the production of metabolites. Reducing the activity of wake promoting neurons represents the active process of sleep initiation. Metabolite-dependent neuronal activity is known as metabolite homeostasis (Datta, 2010). Lately, electrophysiological studies have suggested that the thalamic reticular nucleus is the pacemaker of sleep spindles generation (Steriade, McCormick, & Sejnowski, 1993). The thalamic reticular nucleus consists exclusively of GABAergic neurons, it also serves as the sensory and internal signal at the gateway to the cerebral cortex. The thalamic reticular nucleus contains two different types of neurons; the thalamo-cortical relay neurons which relay incoming sensory signals to the cerebral cortex, and thalamo-reticular neurons which prevents the formal one from sending the sensory signals to the cerebral cortex. During wakefulness, the activity of the thalamo-cortical relay neurons is proportional to the activity of wake promoting noradrenergic, serotonergic, and cholinergic cells, while the thalamic-reticular cells remain inactive. During the passive step of sleep initiation, reduction in wake-promoting cells leads to reduction in activity of thalamo-cortical relay and enhancement of the thalamic-reticular cell. Excitation of thalamic-reticular relay further inhibits thalamo-cortical relay by activation of the inhibitory postsynaptic GABA-B receptors. Therefore, the gate for cerebral cortex sensory signals is closed and the cerebral cortex is deprived of external information, which is reflected by high voltage and slow brain waves in NREM sleep, an indication of cortical inactivity (Datta, 2010; Kalia, 2006; Stenberg & Porkka-Heiskanen, 1990).

Sleep occurs in all organisms with neuronal/glial network, suggesting that sleep is a property of every neuronal network. While many theories have been presented to explain the function of sleep such as; energy restoration, waste elimination, thermoregulation, and neuronal connectivity and plasticity augmentation, sleep is still a challenging enigma for scientists

(Krueger, Frank, Wisor, & Roy, 2016; Krueger & Obal, 2003). Overall, sleep is essential for optimum health, and particularly for optimal mental health as discussed below.



3. Sleep and mental health

One of the leading theories of sleep function is the synaptic homeostasis. The synaptic homeostasis hypothesis proposes that; extensive strengthening of synapses during wakefulness increases the need for energy resources and hence saturates learning processes (Ringli & Huber, 2011; Tononi & Cirelli, 2014). During sleep, spontaneous neuronal activity normalizes the synaptic strength and restores the cellular homeostasis. The synchronized neuronal activity during sleep forms high amplitude slow oscillation reflected by increased SWA in EEG. Slow wave oscillation results from repeated sequences of depolarization and hyperpolarization which leads to reduction in synaptic strength. Ultimately, this leads to reduction in synaptic strength which reduces the amplitude and the synchronization of the slow oscillation reflected by the decrease of the SWA with time after sleep. Hence, by recalibrating synaptic strength to the baseline level, sleep promotes synaptic homeostasis (Ringli & Huber, 2011; Tononi & Cirelli, 2014). Accordingly, sleep plays an essential role in energy restoration and neuronal plasticity and connectivity. And, neuronal plasticity underlies sleep-dependent memory consolidation. In fact, many studies have linked alterations of sleep dependent-plasticity and memory functions to neurobehavioral and psychiatric disorders especially when sleep deprivation occurred during developmental stages of early life.

Another proposed function of sleep is the regulation of affective brain function. Neuroimaging studies have showed that the activity of the emotion related brain regions including the amygdala, striatum, hippocampus, and the prefrontal cortex increases during REM sleep. Enhanced activity of emotional regulation regions is associated with reduction in level of adrenergic locus coeruleus tone during REM sleep (Dang-Vu et al., 2010; Kametani & Kawamura, 1990; Ouyang, Hellman, Abel, & Thomas, 2004). This is important because affective experiences are associated with burst of adrenergic tone during the time of traumatic and/or stressful experiences. Elevation of adrenergic tone and autonomic reactions tag these affective experiences with emotion forming salient emotional memory (Goldstein & Walker, 2014). During REM sleep, this emotional memory is recalled

with reduced adrenergic tone leading to decoupling of emotions from the information of the experience. Removal of the affective emotions that originally tagged the emotional experiences is a preventive mechanism from developing anxiety disorders that result from persistence of affective charges within memory networks. Hence, the emotional regulation function of sleep is considered as a mechanism to forget the emotional tone of affective experiences, while retaining the memory of those experiences (Goldstein & Walker, 2014). Additionally, several studies have suggested that reduction of the locus coeruleus activity during REM sleep recalibrates next day noradrenergic response to emotional stimuli. This allows a balance between emotional sensitivity and specificity to salient stimuli governed by top-down prefrontal cortex control of the amygdala (Goldstein & Walker, 2014; Hermans et al., 2011; Mallick & Singh, 2011; van Marle, Hermans, Qin, & Fernandez, 2009). Emotional regulation function of sleep might explain the complex relationship between sleep, sleep deprivation and psychiatric disorders.



4. Consequences of sleep deprivation

While sleep has an essential role in maintenance of body and brain functions, consequently, sleep deprivation (SD) has been associated with many physiological and psychological disorders. For example, in healthy individuals, SD has been linked to metabolic disorders including diabetes 2 and obesity (Knutson, Spiegel, Penev, & Van Cauter, 2007), and increased the risk of cardiovascular diseases (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011; Dettoni et al., 2012). The association between SD and mental health has been suggested in many clinical and epidemiological studies. The detrimental effects of SD on memory encoding and learning have been extensively reported in human and animal studies (Drummond et al., 2000; Guan, Peng, & Fang, 2004; Harrison & Horne, 2000). Moreover, in both human and animal models of fear conditioning, SD negatively affects fear extinction following exposure to traumatic event contributing to development of post-traumatic stress disorder (PTSD) (Pace-Schott, Germain, & Milad, 2015). Additionally, affective disorders including anxiety and depression are highly correlated with sleep loss (Babson, Trainor, Feldner, & Blumenthal, 2010; Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). We will discuss studies implicating sleep loss with several mental impairments including depression, anxiety disorders and cognitive impairment.

4.1 Sleep deprivation and depression

Several epidemiological studies have indicated the remarkable link between sleep and psychiatric disorders. For instance, 75% of depressed subjects have insomnia symptoms, and 20% of patients with insomnia experienced depressive symptoms (Nutt, Wilson, & Paterson, 2008; Tsuno, Besset, & Ritchie, 2005). Furthermore, sleep EEG in depressed patients showed alterations in sleep architecture including; a decrease in REM latency (the time from sleep start and first period of REM), an increase in total REM sleep time and density, and reduction in slow wave sleep (SWA), additionally, high risk studies including relatives of depressed patients indicated that REM sleep alterations may precede the onset of depression and hence, might be useful in identifying subjects at high risk for depression (Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013). In fact, one hypothesis has suggested the involvement of REM sleep dysregulation in the etiology and pathophysiology of depression (Palagini et al., 2013). Indeed, prospective studies have suggested that sleep deprivation in adolescents increases the risk for major depression which in turn increases the risk of sleep reduction (Roberts & Duong, 2014). Data from animal studies suggest that chronic sleep restriction may gradually induce changes in neuroendocrine stress systems, serotonergic neurotransmission, neurogenesis and neuronal plasticity (Meerlo, Havekes, & Steiger, 2015). Alteration of synaptic plasticity and strength by chronic SD might lead to alteration in connectivity within the different brain regions involved in the regulation of emotion and mood contributing to the pathophysiology of depression (Meerlo et al., 2015; Meerlo, Sgoifo, & Suchecki, 2008).

4.2 Sleep deprivation and anxiety disorders

In healthy adults, acute sleep deprivation is reported to increase self-reported symptoms of affective psychopathology (Babson et al., 2010; Kahn-Greene et al., 2007). Some studies have suggested that anxiety disorders and sleep problems are prevalent and comorbid. In a German survey, examination of the relationships between anxiety disorders and sleep quality revealed that most anxiety disorders are moderately associated with poor sleep quality. Moreover, individuals with anxiety disorders and poor sleep have compromised mental health and increased disability relative to those with anxiety disorders alone (Ramsawh, Stein, Belik, Jacobi, & Sareen, 2009). Other studies have suggested that sleep disturbance might contribute to anxiety disorders and it might exacerbate the severity of the symptoms in

anxiety and related disorders. Sleep disturbance may also diminish treatment efficacy in these disorders suggesting that addressing sleep problems in the treatment of anxiety disorders may enhance treatment efficacy (Cox & Olatunji, 2016).

Animal models of SD are very important for investigating the link between sleep deprivation and anxiety, however, the effect of SD on anxiety produced inconsistent results in rodents. Some studies have reported that SD induces anxiety-like behavior, while others have reported reduced anxiety-like behavior following SD which makes it hard to reproduce sleep deprivation-induced anxiety in humans (Pires, Bezerra, Tufik, & Andersen, 2016). The lack of consistency in animal models, might be attributed to the variation of SD methods and protocols used (Alkadhi, 2013), or the lack of the sensitivity of methodologies used for the evaluation of the anxiety-like behavior (Pires et al., 2016). With respect to the methodology, some studies have suggested the analysis of self-grooming for evaluation of anxiety-like behavior following SD (Pires et al., 2012; Pires, Tufik, & Andersen, 2013).

4.3 Sleep deprivation and cognitive impairments

Impairment of memory processing by sleep loss has been addressed in human and animal models of SD (Havekes, Vecsey, & Abel, 2012). In humans, functional magnetic resonance imaging (fMRI) studies involved sleep-deprived and well-rested brains clearly demonstrated the importance of sleep for optimal cognitive function and learning (Chee & Chuah, 2008). Chronic sleep-restriction experiments which mimic sleep loss experienced by many individuals in modern societies and by individuals with sleep disorders demonstrate that over time, cognitive deficits accumulate to severe levels. Functional neuroimaging has revealed that sleep deprivation associated cognitive deficits, involve scattered changes in the brain regions including frontal and parietal control areas, secondary sensory processing areas, and thalamic areas. However, the degree of cognitive vulnerability to sleep loss varies among individuals which may be attributed to the basis of genes involved in sleep homeostasis and circadian rhythms (Goel, Rao, Durmer, & Dinges, 2009). Animal models of SD provided useful insights for the molecular processes that might play a role in interaction between sleep and memory. SD studies indicate that hippocampus-dependent memory formation and working memory are mainly sensitive for SD, and that there is a specific period of time following training during which SD impacts memory consolidation. The most sensitive period for SD was found to be 5–6 h

following training, however, the sensitive period varied depending on the nature of the training (Havekes et al., 2012). Electrophysiological studies were conducted both in vivo and in vitro to determine the effect of SD on hippocampal synaptic plasticity. SD was reported to inhibit synaptic potentiation in the hippocampus but facilitating certain forms of synaptic depression (Hagewoud et al., 2010; Kopp, Longordo, Nicholson, & Luthi, 2006). And brief period of SD (5–6 h) impairs the maintenance of long-term potentiation (LTP). LTP is a form of synaptic plasticity critical for memory consolidation which depends on cyclic AMP (cAMP) and protein kinase a (PKA) pathway. The cAMP–PKA pathway, by phosphorylation of GluA1 subunit of α -amono-3-hydroxy-methyl-4-isoxazole propionic acid receptors (AMPArs), controls AMPAR function and hence, synaptic plasticity. Long periods of total SD impaired spatial working memory and reduced phosphorylation of GluA1 in mice hippocampus (Hagewoud et al., 2010). Additionally, cAMP–PKA pathway and the MAP kinase (MAPK) pathway represented by the extracellular signal-regulated kinase (ERK), together, those pathways regulate changes in synaptic efficacy which is essential for memory formation. Seventy five hours of REM sleep deprivation using platform over water method, decreased synaptic plasticity and transmission which were associated with reduced ERK phosphorylation and GluA1 expression in mice hippocampus (Ravassard et al., 2009). The role of protein synthesis in sleep-dependent cortical plasticity during memory consolidation has been suggested by several studies (Sweatt & Hawkins, 2016). Translational initiation is a critical step in protein synthesis which involves the translation initiation factors 4E and 4G in eukaryotes (eIF4E and eIF4G). In the brain, eIF4E is sequestered by 4E binding protein 2 (4EBP2) which prevents its interaction with eIF4G. The rapamycin complex 1 (mTORC1) is essential for release of eIF4E by phosphorylation of 4EBP2 allowing eIF4E–eIF4G binding and subsequent protein synthesis initiation (Sweatt & Hawkins, 2016). A series of experiments have demonstrated that protein synthesis regulated by mTORC1-dependent dephosphorylation of 4EBP2 is a critical signaling mechanism that underlies memory deficits induced by sleep loss (Graves, Heller, Pack, & Abel, 2003; Hernandez & Abel, 2008; Tudor et al., 2016). In summary, SD impacts memory and cognition potentially through alteration of synaptic plasticity and protein synthesis in critical brain regions including hippocampus and prefrontal cortex. The molecular mechanisms by which SD alters protein synthesis and synaptic plasticity is not fully addressed, oxidative stress and inflammation might have a role in such mechanisms, more details are discussed in this review.



5. Sleep deprivation in children and adolescents

According to a national survey conducted in 2014 by the National Sleep Foundation, approximately 55% of children and adolescents don't obtain adequate sleep per night. Further, inadequate sleep is more common at older ages; for example, 31% of children 6–11 years old sleep less than the recommended 11 h per night, while 56% of adolescents 15–17 years old sleep less than the recommended sleep hours per night (Buxton et al., 2015) (National Sleep Foundation, 2014 sleep in America poll). Comparisons between cross sectional studies conducted between 2003 and 2012 by the National Survey of Children's Health on children 6–17 years old (Hawkins & Takeuchi, 2016) found a consistent increase of inadequate sleep among all studied age groups, and the shorter sleep duration increased with age. Sleep deprivation in youth has been associated with adverse physical, mental and behavioral outcomes, therefore, increasing the amount of sleep in youth has become a public health priority in the United States. In fact, members of the American Academy of Sleep medicine have released a consensus statement of recommended amount of sleep for youth to promote optimal physical and mental health (Paruthi et al., 2016). Several studies investigated the causes of a decrease in sleep duration among youth. Bedtime delay and short sleep duration in school-aged children and adolescents, have been consistently related to the extensive exposure of electronic media including television viewing, use of computers, electronic gaming, mobile telephones, and music (Cain & Gradisar, 2010). Early school start times and academic workload are also lead to insufficient sleep in school aged children and adolescents (Wheaton, Chapman, & Croft, 2016). Furthermore, sleep disturbances are common among youth with psychiatric disorders such as anxiety, depression, autism, or schizophrenia (Alfano, Pina, Zerr, & Villalta, 2010; Gregory & Sadeh, 2016; Hodge, Carollo, Lewin, Hoffman, & Sweeney, 2014; Yilmaz, Sedky, & Bennett, 2013) and in children who exposed to violent events (Spilsbury, Babineau, Frame, Juhas, & Rork, 2014). The detrimental effects of insufficient sleep in youth on mental and behavioral outcomes have been reported in many epidemiological and clinical studies, some are discussed in the next section.

5.1 Consequences of sleep deprivation in children and adolescents

In otherwise healthy children, insufficient sleep has been linked to poor school performance (Astill et al., 2012; Dewald et al., 2010), behavioral

problems such as attention deficit, and emotional symptoms such as anxiety and depression (Gregory & Sadeh, 2012; Maski & Kothare, 2013). In a longitudinal study, sleep deprivation in children 2.5–6 years old was associated with hyperactivity and poor behavior at school (Touchette et al., 2008, 2009). Later onset of anxiety and depression are also associated with early life (childhood and adolescent) sleep disturbances (Gessa et al., 1995; Gregory et al., 2005). The longitudinal studies suggest that early life sleep deprivation are highly predictive of future affective and behavioral problems (Maski & Kothare, 2013). How sleep at early life modulate neurobehavioral functioning and cognition is not fully understood. Some investigators have suggested that sleep spindles and slow wave activity, which show significant changes through childhood and adolescents might have a role in neurobehavioral and executive functional development. However, further research are needed to investigate the association between sleep and neurobehavioral development (Kurth, Olini, Huber, & LeBourgeois, 2015; Lopez, Hoffmann, & Armitage, 2010; Maski & Kothare, 2013).



6. Neurobiological processes and early life sleep deprivation

6.1 Sleep and postnatal brain development

Brain development starts prenatally and continues postnatally in all mammals. Postnatal brain development is characterized by cortical gray matter expansion/regression and white matter development. Gray matter maturation is indicated by a massive increase of synapse (synaptogenesis), that peaks at childhood (2–3 years old) followed by rapid elimination and refinement of excess synapses (synaptic pruning) which continues until adolescent stage. However, the increase in synaptic density and synaptic pruning is regionally specific, for instance, synaptic density peaks in visual cortex at 6–8 months of age, while in prefrontal cortex at age of 2–4 years. White matter development is indicated by neuronal myelination which occur during early life stages (childhood and adolescence) and continues until early adult stage. These processes are important for optimization of neuronal connectivity and maturation of neurobehavioral functions (Huttenlocher, 1979; Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013).

Interestingly, sleep architecture shows remarkable changes during development that parallel the time course of postnatal brain maturation,

suggesting a relationship between postnatal brain development and sleep (Kurth et al., 2015; Semple et al., 2013). REM sleep is highly concentrated in newborns consisting around 50% of their total sleep. During the first two years of life, REM sleep diminishes to 20%–25% of total sleep time that maintained throughout development (Louis, Cannard, Bastuji, & Challamel, 1997). REM sleep found to promote cortical plasticity necessary for consolidation of waking experiences in developing brain (Dumoulin Bridi et al., 2015). Furthermore, localization, distribution and coherence of sleep EEG from early childhood to late adolescence reflect the brain maturational processes. Cortical maturation follows a posterior to anterior trajectory, similarly, SWA shifts from posterior to anterior brain regions with maturation (Kurth, Ringli, et al., 2010). In addition, the coherence of EEG activity, which measures the functional connectivity strengthen by neuronal myelination, increases with maturation in a region-specific manner (Kurth, Achermann, Rusterholz, & Lebourgeois, 2013; Tarokh, Carskadon, & Achermann, 2010). Myelination is important for brain connectivity and functional network maturation. Oligodendrocytes wrap the axons with myelin sheaths forming multiple insulating layers that increase the action potential conduction by 1000-folds. Neuronal myelination is reflected by the increase of the volume of the white matter in the brain. In humans, neuronal myelination started prenatally and continues through the early adult life. In rodents, neuronal myelination continues until at least postnatal day (PND) 30–40. Interestingly, oligodendrocytes proliferation and myelin synthesis occur preferentially during sleep (Toth & Neumann, 2013), which suggests that neuronal activity during sleep, by inducing neuronal myelination, enhances functional connectivity during brain development (Kurth et al., 2013, 2015). Hence, sleep is essential for neuronal network connectivity and brain maturation during the sensitive window of childhood.

Another important process during postnatal brain development is synaptogenesis. Synaptogenesis is the process of formation of new synapses between neurons. During brain development, there is a period of synapse overproduction followed by synapse pruning and elimination. These processes reflect the refinement of neuronal circuits during childhood and adolescence inducing synaptic plasticity and cortical maturation essential for efficient processing of adult cognition. In humans, density of synapses increases rapidly after birth to reach 50% over the adult level by age of 2–3 years (Huttenlocher, 1979; Huttenlocher, 1984; Huttenlocher & Dabholkar, 1997; Huttenlocher, de Courten, Garey, & Van der Loos,

1982). In rodents, synaptic density peaks during the second week after birth and reaches the adult level by week 3–4 of age (Crain, Cotman, Taylor, & Lynch, 1973; Semple et al., 2013). However, the timing of appearance of synapse peak and elimination is region specific. The increase in synaptic density is correlated with the increase of N-Methyl-D-Aspartic Acid Receptors (NMDARs) density in the cortex which peaks at age of 1–22 years in humans and at PND28 in rats (McDonald, Johnston, & Young, 1990; Zhang, 2006; Zhong, Carrozza, Williams, Pritchett, & Molinoff, 1995). Interestingly, Studying the synaptic density using two-photon microscopy in adolescent mice showed that sleep is associated with a net of cortical spine loss while net gain of spine was increased during wakefulness, (Maret, Faraguna, Nelson, Cirelli, & Tononi, 2011). Furthermore, in a longitudinal study of sleep EEG across childhood and adolescence, (Campbell & Feinberg, 2009; Feinberg & Campbell, 2010), a very steep decline of NREM delta and theta waves was reported during adolescent stage (11–16.5 years). The study suggested that EEG changes might reflect synaptic pruning indicated by reduction in cortical thickness as measured by MRI in adolescents (Shaw et al., 2008). In a cross sectional study including children and adolescents, the topography of SWA was highest over the posterior brain region in children then shifted to the frontal cortex in adolescents, which matches the course of gray matter maturation (Kurth, Jenni, et al., 2010; Smith, Wilkins, Mogavero, & Veenema, 2015). The fact that SWA amplitude increases during childhood to reach maximum during puberty, then decreases during adolescence, suggests that SWA might be the driving mechanism underlying brain maturation processes (Ringli & Huber, 2011). Indeed, measuring the cortical volume and the synaptic density across development in humans and rats found a clear correlation between the trajectories of SWA coherence and cortical maturation (Kurth et al., 2015). This proposed role of SWA in brain maturation is further strengthened by the emergence of synaptic homeostasis hypothesis mentioned above. Hence, SWA can be an indicator of synaptic density and strength during development (Ringli & Huber, 2011). Cortical maturation is also correlated with progressive changes in behavioral and cognitive functions from childhood to adulthood, this behavioral and cognitive development is thought to rely on synaptic pruning and neuronal myelination (Luna & Sweeney, 2004), supporting the link between SWA, cortical maturation and behavioral development. Therefore, this window of development is highly sensitive to sleep deprivation. Yet the exact relationship between brain maturation, SWA and behavior needs further investigation, as several

neurobehavioral disorders are associated with sleep problems, suggesting a bidirectional relationship between sleep and neurobehavioral disorders.



7. Sleep deprivation and allostatic load

Allostatic load is a measure of cumulative physiological dysregulation across biological systems. Allostasis is the process of maintaining homeostasis, it is an active process that involves metabolic mediators such as those of the autonomic nervous system, the neuroendocrine system and the immune system (McEwen & Wingfield, 2003). Chronic stress or deficits of homeostasis regulating systems enhance allostatic load/overload promoting brain and body dysfunction (McEwen & Stellar, 1993; McEwen & Wingfield, 2003). Consequences of SD and circadian disruption involves elevation of allostatic load mediators such as, pro-inflammatory cytokines, cortisol, oxidative stress, glycogen, and insulin (Hirotsu, Tufik, & Andersen, 2015; McEwen, 2006). Accordingly, SD is reported to induce hypertension, reduce parasympathetic tone, increase risk for obesity, and increase risk of cardiovascular diseases and diabetes (Hirotsu et al., 2015). The consequences of sleep deprivation suggested that SD is a stressor that contribute to allostatic load leading to physiological and behavioral dysfunction and precipitation of physiological and psychological diseases (McEwen, 2006; McEwen & Karatsoreos, 2015).



8. Sleep deprivation, oxidative stress and inflammation

Oxidative stress occurs when the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) overwhelms the antioxidant capacity of the cells (Betteridge, 2000). ROS and RNS comprise of free radical species and non-radical species/oxidants (Pham-Huy, He, & Pham-Huy, 2008). Free radicals are molecules or atoms with unpaired electrons in their outer shell such as superoxide ($O_2^{\cdot-}$), hydroxyl ($OH^{\cdot}$), peroxy ($ROO^{\cdot}$), nitric oxide ($NO^{\cdot}$) and nitrogen dioxide ($NO_2^{\cdot}$). Free radicals are highly unstable and readily participate in further reactions forming non-radical species that are also called oxidants. Examples of non-radical species are peroxynitrite ($ONOO^-$), hydrogen peroxide (H_2O_2), ozone (O_3), hypochlorous acid ($HOCl$), nitrous acid (HNO_2), etc. These non-radicals in turn can easily produce free radicals by losing one or more electrons (Halliwell, 2007).

Normally, ROS and RNS are produced in the body as a consequence of redox reactions that accompany different metabolic processes such as oxidative phosphorylation, prostaglandin synthesis or various enzymatic reactions that involve cytochrome P450 enzyme complex (Pacher, Beckman, & Liaudet, 2007). Activation of pathways associated with inflammation, stress, and aging also result in production of ROS and RNS. At physiologically low to moderate levels, ROS and RNS play significant roles in performing different cellular functions and are critical for optimum cellular health. For instance, ROS/RNS participate in various signaling process and cascades in cardiac, epithelial, vascular and neuronal cells. Nitric oxide is an example of oxidant which serves as an intercellular signaling molecule that regulates dilation of arteries, clotting of blood, gastric motility and transmission between neurons (Pacher et al., 2007). Also, ROS plays an important role in LTP which is a form of synaptic plasticity considered essential for learning and memory (Serrano & Klann, 2004). ROS causes activation of mitogen activated protein kinases (MAPKs), protein kinases that regulate cellular signal transduction (Son et al., 2011). Moreover, ROS are also a critical part of cellular immune response as they lead to activation of proinflammatory cytokines such as IL-1 β and TNF- α (Arsenijevic et al., 2000; Wang, Malo, & Hekimi, 2010). Oxidants such as H₂O₂ oxidize proteins thereby altering their structure and function which then leads to transcription of specific genes or activates certain signaling cascades that regulate normal cellular proliferation, maturation or controlled degradation (Reczek & Chandel, 2015; Schieber & Chandel, 2014).

Generally, antioxidant defense systems in the body ensure that ROS and RNS production in the body is just enough to achieve physiologically beneficial effects. The antioxidant defense mechanisms include enzymatic and non-enzymatic systems. Enzymatic antioxidant defenses include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Non-enzymatic antioxidants include ascorbic acid (Vitamin C), α -tocopherol (Vitamin E), glutathione (GSH), carotenoids, flavonoids, and others. SOD exists in two forms: cytosolic Cu/Zn-SOD, and mitochondrial Mn-SOD. SOD catalyzes the dismutation of the highly reactive superoxide anion O₂⁻ to the less reactive species; H₂O₂ and O₂. Hydrogen peroxide can be destroyed by CAT or GPX reactions. CAT reacts very efficiently with H₂O₂ to form water and molecular oxygen. Glutathione peroxidase (GPx) catalyzes the reduction of hydro peroxides using GSH (Kleinova et al., 2007). Glutathione system is one of the most essential anti-oxidative defense mechanisms. Glutathione (GSH) is a tripeptide that contains

L-cysteine, L-glutamic acid and glycine. Glutathione exists in reduced (GSH) and oxidized (GSSG) states. Reduced glutathione (GSH) is a major antioxidant molecule in cells. It provides reducing equivalents for the GPx which results in formation of a disulfide bond between two GSH molecules generating oxidized glutathione (GSSG). The enzyme glutathione reductase (GSR) recycles GSSG to GSH (Masella, Di Benedetto, Vari, Filesi, & Giovannini, 2005).

In normal conditions, there is a balance between pro-oxidant production and the intracellular levels of antioxidants. This balance is essential for the survival of organisms and their health (Valko et al., 2007). However, various factors lead to excessive production of these reactive species setting off the balance maintained by the antioxidants, thus resulting in oxidative stress. Once the levels of ROS and RNS increase beyond an optimum level, the resultant oxidative stress leads to cellular damage by oxidizing lipids, proteins and DNA. Oxidative stress-associated cellular damage and alteration of cellular components initiates a cascade of underlying mechanisms that eventually lead to different diseases. Increase in oxidative stress induces an inflammatory response via release of proinflammatory cytokines such as TNF- α and IL-6. Other mediators of inflammation such as nuclear factor-kappa B (NF- κ B), vascular cell adhesion molecule-1 (VCAM-1) are also activated by ROS and RNS. This inflammatory response is an underlying causal mechanism for various diseases such as diabetes, chronic renal failure, hypertension, chronic obstructive pulmonary diseases (COPD) and rheumatoid arthritis as well as neurodegenerative disorders like Parkinson's disease and multiple sclerosis (Aruoma, Grootveld, & Bahorun, 2006; Butterfield, Castegna, Drake, Scapagnini, & Calabrese, 2002; Hoshino & Mishima, 2008; MacNee, 2001; Prabhakar, 2013).

The central nervous system (CNS) is especially vulnerable to the effects of oxidative stress owing to relatively low level of antioxidants in the brain and high level of transition metals such as Fe²⁺ that form reactive unstable complexes and generate more free radicals (Rahal et al., 2014). Also, levels of polyunsaturated fatty acids (PUFAs) and lipids are very high in the CNS. These lipids and PUFAs are well-known targets of oxidative stress and undergo free-radical induced lipid peroxidation and oxidation (Cherubini, Ruggiero, Polidori, & Mecocci, 2005). Moreover, various redox reactions that result in production of ROS and RNS occur in the brain in order to meet the high oxygen and energy requirement of the brain (Butterfield et al., 2002). Therefore, it seems likely that excessive levels of ROS and RNS in the brain might alter the structure and function of different brain

regions resulting in neurological and psychological conditions. However, neuronal response to oxidative stress is not uniform, which makes some regions of the brain more vulnerable to oxidative stress than others. For example, it has been reported that the cortex and the hippocampus are the most sensitive brain regions to oxidative stress (Wang & Michaelis, 2010).

Both clinical and preclinical studies have indicated that behavioral and memory deficits are associated with oxidative stress elevation. For example, in an animal model of stress, elevation in markers of oxidative stress in hippocampus of socially defeated rats was associated with induction of anxiety, depression-like behavior and memory impairment (Patki, Solanki, Atrooz, Allam, & Salim, 2013). Moreover, early life SD increased plasma 8-isoprostane levels and induced expression of antioxidant enzymes in the prefrontal cortex of rats. Elevation of oxidative stress markers was associated with anxiety-like behavior at early life which developed into depression-like behavior at adult life (Atrooz et al., 2019). In humans, depressed patients showed an increase in oxidative stress markers in serum indicated by a decrease in antioxidant enzymes and an increase in the lipid peroxidation marker, malondialdehyde (MDA), as compared to age-matched control group (Stefanescu & Ciobica, 2012). Anxiety disorders in humans were also associated with elevation of lipid peroxidation products and alteration of antioxidant enzymes (Ng, Berk, Dean, & Bush, 2008). Additionally, children and adolescents with anxiety disorders showed plasma elevation of oxidative stress markers (Guney et al., 2014).

One of the proposed functions of sleep is promoting anti-oxidative mechanisms. This perhaps is an adaptive response to sleep loss/deprivation as SD or sleep loss might induce oxidative stress. For instance, it has been suggested that sleep promotes removal of free radicals accumulated during wakefulness (Reimund, 1994). Peroxide infusion into preoptic/anterior hypothalamus region of brain induced sleep in rats by promoting the release of neuromodulators, nitric oxide and adenosine (Ikeda et al., 2005). Furthermore, intraventricular infusion of the oxidized glutathione (GSSG) enhanced the SWA sleep and REM sleep (Honda, Komoda, & Inoue, 1994). Indeed, some studies have suggested that oxidative stress is the underlying pathophysiological mechanism for development of cardiovascular and neurobehavioral complications mediated by obstructive sleep apnea (Gozal & Kheirandish-Gozal, 2008). Animal models also have provided important insights into the relationship between oxidative stress and sleep deprivation (Villafuerte et al., 2015). Chronic SD in rats decreased SOD activity in the

hippocampus and brainstem (Ramanathan, Gulyani, Nienhuis, & Siegel, 2002), and decreased total glutathione (GSH) levels and catalase activity in liver, but increased glutathione peroxidase (GPx) activity in the heart (Everson, Laatsch, & Hogg, 2005). Short periods of SD (96 h) decreased the GSH levels in rats' hippocampus (D'Almeida et al., 1998). Twenty four hours sleep deprivation in rats reduced lipid peroxidation in hippocampus (Melgarejo-Gutierrez et al., 2013) and increased the level of glyoxalase (GLO-1) and glutathione reductase (GSR-1) in prefrontal cortex, hippocampus, and amygdala (Vollert et al., 2011). While acute SD (6 h) in rats by gentle handling increased the level of the reduced glutathione (GSH) levels in the cortex, brain stem, and forebrain and enhanced the activity of GPx in hippocampus and cerebellum (Ramanathan, Hu, Frautschy, & Siegel, 2010). Prolonged SD, for 5–11 days, significantly decreased SOD activity in hippocampus and brain stem of adult rats (Ramanathan et al., 2002). Adult rats exposed to 24 h SD showed behavioral and cognitive deficits associated with plasma elevation of 8-isoprostane (Solanki, Atrooz, Asghar, & Salim, 2016). However, other animal models of SD did not find any changes in oxidative stress markers or antioxidant capacity in peripheral blood or brain regions following SD (D'Almeida et al., 1997; Gopalakrishnan, Ji, & Cirelli, 2004). The inconsistency of results might due to the variation in the methods used for sleep deprivation, the duration of SD, or the rodent strains used for SD. Collectively, these data suggest that while short periods of SD enhance anti-oxidant response in brain and other organs, long SD periods reduce the anti-oxidant response suggesting that extended wakefulness induces chronic oxidative stress that lead to failure of antioxidant mechanisms to sustain the accumulation of pro-oxidants.

Moreover, SD has been implicated in inflammation and immune dysfunction. In healthy individuals, acute or chronic SD is associated with increased serum levels of IL-1, TNF- α , IL-6, IL-17, and NF κ B, in addition to alteration of numbers and activity of macrophages and natural killer cells (Irwin et al., 2008, 2015; van Leeuwen et al., 2009; Wright Jr et al., 2015). In preclinical studies, SD induced elevation of inflammatory markers such as; IL-1, IL-6, and TNF- α , in peripheral blood and different brain regions, also has been reported (Atrooz et al., 2019; Chennaoui et al., 2015). While the immune system has the potential to induce brain plasticity and neuronal networks functioning, elevation of neuroinflammatory mediators can cause impairment of synaptic plasticity (Hong, Mills, Loreda, Adler, & Dimsdale, 2005; Tancredi et al., 2000). In rat's hippocampus slices, treatment with IL-6 decreased the synaptic plasticity indicated by reduction of LTP potentially

through inhibition of MAP/ERK activation. The effect of IL-6 on the synaptic plasticity was associated with the activation of the signal transducer and activator of transcription-3 (STAT3), Phosphorylation of STAT3 is mediated via gp 130-associated JAK tyrosine kinases, accordingly, inhibition of synaptic plasticity by IL-6 was counteracted by simultaneous treatment with the tyrosine kinases inhibitor lavendustin A, while inactivation of MAP/ERK might be mediated by stimulation of tyrosine and/or dual-specificity phosphatases (Tancredi et al., 2000).

In vitro studies showed that as a response to oxidative stress, the activity of P38 and JNK MAPKs increased which in turn mediated the production of pro-inflammatory cytokines including IL-6. Additionally, activation of the MAPKs pathway was also essential for regulating the expression of the antioxidant enzymes including HO and Mn-SOD (Nahimyj, Livne-Bar, Guo, & Sivak, 2013). Prolonged activation of MAPKs is detrimental to cells due to their role in mediating biosynthesis of proinflammatory cytokines, hence, activation of MAPKs, induces the expression of MAPK phosphatases such as (MKP1) which in turn dephosphorylates MAPKs and therefore restrains the MAPKs-mediated inflammatory response (Collins, Downer, Toulouse, & Nolan, 2015). This mechanism of negative feedback regulation is critical for cell survival. Hence, MKP1 is considered as a key factor in regulating the stress response, and its expression is highly regulated transcriptionally, post-transcriptionally, and post-translationally by numerous factors (Kuwano & Gorospe, 2008). It is well known that MKP1 regulates the magnitude and duration of MAPKs signaling, and as the strength of MAPKs signaling determines the duration of biological responses and many physiological outcomes, therefore, the spatial and temporal titration of MKP1 has a fundamental regulatory role. MKP1, by dephosphorylation of ERK_{1/2} and MEK, alters the neurotrophic downstream signaling pathway which is essential for neuronal growth, plasticity and cell survival (Duman, 2004; Valjent, Caboche, & Vanhoutte, 2001). Interestingly, in rat models of early life SD, SD caused enhanced expression of MKP1 and also caused long lasting reduction in synaptic density and plasticity in rats prefrontal cortex that was evident at adult stage (Atrooz et al., 2019).

In summary, while sleep has a role in regulation of synaptic plasticity and protein synthesis, sleep deprivation might alter protein synthesis, and synaptic plasticity through oxido-inflammatory mechanisms. During early developmental stage, synaptic growth and synaptic plasticity are essential for neural circuit formation and maturation, therefore SD during these critical periods might permanently alter neural circuit maturation in brain regions

that regulate emotion and cognition leading to development of psychiatric disorders later in life.

Disclosure of interest

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References

- Abrahamson, E. E., & Moore, R. Y. (2006). Lesions of suprachiasmatic nucleus efferents selectively affect rest-activity rhythm. *Molecular and Cellular Endocrinology*, 252(1–2), 46–56. <http://dx.doi.org/10.1016/j.mce.2006.03.036>.
- Alfano, C. A., Pina, A. A., Zerr, A. A., & Villalta, I. K. (2010). Pre-sleep arousal and sleep problems of anxiety-disordered youth. *Child Psychiatry and Human Development*, 41(2), 156–167. <http://dx.doi.org/10.1007/s10578-009-0158-5>.
- Alkadhi, K. (2013). Neurobiological consequences of sleep deprivation. *Current Neuropharmacology*, 11, 19.
- Arsenijevic, D., Garcia, I., Vesin, C., Vesin, D., Arsenijevic, Y., Seydoux, J., & Richard, D. (2000). Differential roles of tumor necrosis factor-alpha and interferon-gamma in mouse hypermetabolic and anorectic responses induced by LPS. *European Cytokine Network*, 11(4), 662–668.
- Aruoma, O. I., Grootveld, M., & Bahorun, T. (2006). Free radicals in biology and medicine: From inflammation to biotechnology. *BioFactors*, 27(1–4), 1–3.
- Astill, R. G., Van der Heijden, K. B., Van Ijzendoorn, M. H., & Van Someren, E. J. (2012). Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed. *Psychological Bulletin*, 138(6), 1109–1138. <http://dx.doi.org/10.1037/a0028204>.
- Atrooz, F., Liu, H., Kochi, C., & Salim, S. J. N. (2019). *Early life sleep deprivation: Role of oxidative-inflammatory processes*.
- Babson, K. A., Trainor, C. D., Feldner, M. T., & Blumenthal, H. (2010). A test of the effects of acute sleep deprivation on general and specific self-reported anxiety and depressive symptoms: An experimental extension. *Journal of Behavior Therapy and Experimental Psychiatry*, 41(3), 297–303. <http://dx.doi.org/10.1016/j.jbtep.2010.02.008>.
- Betteridge, D. J. (2000). What is oxidative stress? *Metabolism*, 49(2 Suppl. 1), 3–8.
- Borbely, A. A. (1982a). Sleep regulation. Introduction. *Human Neurobiology*, 1(3), 161–162.
- Borbely, A. A. (1982b). A two process model of sleep regulation. *Human Neurobiology*, 1(3), 195–204.
- Butterfield, D. A., Castegna, A., Drake, J., Scapagnini, G., & Calabrese, V. (2002). Vitamin E and neurodegenerative disorders associated with oxidative stress. *Nutritional Neuroscience*, 5(4), 229–239. <http://dx.doi.org/10.1080/10284150290028954>.
- Buxton, O. M., Chang, A. M., Spilsbury, J. C., Bos, T., Emsellem, H., & Knutson, K. L. (2015). Sleep in the modern family: protective family routines for child and adolescent sleep. *Sleep Health*, 1(1), 15–27. PubMed PMID: 26779564; PubMed Central PMCID: PMC4712736.
- Cain, N., & Gradisar, M. (2010). Electronic media use and sleep in school-aged children and adolescents: A review. *Sleep Medicine*, 11(8), 735–742. <http://dx.doi.org/10.1016/j.sleep.2010.02.006>.
- Campbell, I. G., & Feinberg, I. (2009). Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(13), 5177–5180. <http://dx.doi.org/10.1073/pnas.0812947106>.

- Cappuccio, F. P., Cooper, D., D'Elia, L., Strazzullo, P., & Miller, M. A. (2011). Sleep duration predicts cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *European Heart Journal*, 32(12), 1484–1492. <http://dx.doi.org/10.1093/eurheartj/ehr007>.
- Chee, M. W., & Chuah, L. Y. (2008). Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. *Current Opinion in Neurology*, 21(4), 417–423. <http://dx.doi.org/10.1097/WCO.0b013e3283052cf7>.
- Chennaoui, M., Gomez-Merino, D., Drogou, C., Geoffroy, H., Dispersyn, G., Langrume, C., & Sauvet, F. (2015). Effects of exercise on brain and peripheral inflammatory biomarkers induced by total sleep deprivation in rats. *Journal of Inflammation*, 12, 56. <http://dx.doi.org/10.1186/s12950-015-0102-3>.
- Cherubini, A., Ruggiero, C., Polidori, M. C., & Mecocci, P. (2005). Potential markers of oxidative stress in stroke. *Free Radical Biology and Medicine*, 39(7), 841–852. <http://dx.doi.org/10.1016/j.freeradbiomed.2005.06.025>.
- Cirelli, C. (2006). Cellular consequences of sleep deprivation in the brain. 10(5), 307–321.
- Collins, L. M., Downer, E. J., Toulouse, A., & Nolan, Y. M. (2015). Mitogen-activated protein kinase phosphatase (MKP)-1 in nervous system development and disease. *Molecular Neurobiology*, 51(3), 1158–1167. <http://dx.doi.org/10.1007/s12035-014-8786-6>.
- Cox, R. C., & Olatunji, B. O. (2016). A systematic review of sleep disturbance in anxiety and related disorders. *Journal of Anxiety Disorders*, 37, 104–129. <http://dx.doi.org/10.1016/j.janxdis.2015.12.001>.
- Crain, B., Cotman, C., Taylor, D., & Lynch, G. (1973). A quantitative electron microscopic study of synaptogenesis in the dentate gyrus of the rat. *Brain Research*, 63, 195–204.
- D'Almeida, V., Hipólido, D. C., Azzalis, L. g. A., Lobo, L. c. L., Junqueira, V. n. B., & Tufik, S. J. N. l. (1997). Absence of oxidative stress following paradoxical sleep deprivation in rats. 235(1–2), 25–28.
- D'Almeida, V., Lobo, L. L., Hipólido, D. C., de Oliveira, A. C., Nobrega, J. N., & Tufik, S. (1998). Sleep deprivation induces brain region-specific decreases in glutathione levels. *NeuroReport*, 9(12), 2853–2856.
- Dang-Vu, T. T., Schabus, M., Desseilles, M., Sterpenich, V., Bonjean, M., & Maquet, P. (2010). Functional neuroimaging insights into the physiology of human sleep. *Sleep*, 33(12), 1589–1603.
- Datta, S. (2010). Cellular and chemical neuroscience of mammalian sleep. *Sleep Medicine*, 11(5), 431–440. <http://dx.doi.org/10.1016/j.sleep.2010.02.002>.
- Dettoni, J. L., Consolim-Colombo, F. M., Drager, L. F., Rubira, M. C., Souza, S. B., Irigoyen, M. C., & Lorenzi-Filho, G. (2012). Cardiovascular effects of partial sleep deprivation in healthy volunteers. *Journal of Applied Physiology*, 113(2), 232–236. <http://dx.doi.org/10.1152/japplphysiol.01604.2011>.
- Dewald, J. F., Meijer, A. M., Oort, F. J., Kerkhof, G. A., & Bogels, S. M. (2010). The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. *Sleep Medicine Reviews*, 14(3), 179–189. <http://dx.doi.org/10.1016/j.smrv.2009.10.004>.
- Drummond, S. P., Brown, G. G., Gillin, J. C., Stricker, J. L., Wong, E. C., & Buxton, R. B. (2000). Altered brain response to verbal learning following sleep deprivation. *Nature*, 403(6770), 655–657. <http://dx.doi.org/10.1038/35001068>.
- Duman, R. S. (2004). Role of neurotrophic factors in the etiology and treatment of mood disorders. *NeuroMolecular Medicine*, 5(1), 11–25. <http://dx.doi.org/10.1385/NMM:5:1:011>.
- Dumoulin Bridi, M. C., Aton, S. J., Seibt, J., Renouard, L., Coleman, T., & Frank, M. G. (2015). Rapid eye movement sleep promotes cortical plasticity in the developing brain. *Science Advances*, 1(6), e1500105. <http://dx.doi.org/10.1126/sciadv.1500105>.

- Everson, C. A., Laatsch, C. D., & Hogg, N. (2005). Antioxidant defense responses to sleep loss and sleep recovery. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, 288(2), R374–R383. <http://dx.doi.org/10.1152/ajpregu.00565.2004>.
- Feinberg, I., & Campbell, I. G. (2010). Sleep EEG changes during adolescence: An index of a fundamental brain reorganization. *Brain and Cognition*, 72(1), 56–65. <http://dx.doi.org/10.1016/j.bandc.2009.09.008>.
- Frank, M. G., Issa, N. P., & Stryker, M. P. (2001). Sleep enhances plasticity in the developing visual cortex. *Neuron*, 30(1), 275–287.
- Gessa, G. L., Pani, L., Fadda, P., & Fratta, W. (1995). Sleep deprivation in the rat: An animal model of mania. *European Neuropsychopharmacology*, 5(Suppl. 1), 89–93.
- Goel, N., Rao, H., Durmer, J. S., & Dinges, D. F. (2009). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*, 29(4), 320–339. <http://dx.doi.org/10.1055/s-00029-1237117>.
- Goldstein, A. N., & Walker, M. P. (2014). The role of sleep in emotional brain function. *Annual Review of Clinical Psychology*, 10, 679–708. <http://dx.doi.org/10.1146/annurev-clinpsy-032813-153716>.
- Gopalakrishnan, A., Ji, L. L., & Cirelli, C. (2004). Sleep deprivation and cellular responses to oxidative stress. *Sleep*, 27(1), 27–35.
- Gozal, D., & Kheirandish-Gozal, L. (2008). Cardiovascular morbidity in obstructive sleep apnea: Oxidative stress, inflammation, and much more. *American Journal of Respiratory and Critical Care Medicine*, 177(4), 369–375. <http://dx.doi.org/10.1164/rccm.200608-1190PP>.
- Graves, L. A., Heller, E. A., Pack, A. I., & Abel, T. (2003). Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. *Learning & Memory*, 10(3), 168–176. <http://dx.doi.org/10.1101/lm.48803>.
- Gregory, A. M., Caspi, A., Eley, T. C., Moffitt, T. E., Oconnor, T. G., & Poulton, R. (2005). Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *Journal of Abnormal Child Psychology*, 33(2), 157–163.
- Gregory, A. M., & Sadeh, A. (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews*, 16(2), 129–136. <http://dx.doi.org/10.1016/j.smrv.2011.03.007>.
- Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders—a review of the latest science. *Journal of Child Psychology and Psychiatry*, 57(3), 296–317. <http://dx.doi.org/10.1111/jcpp.12469>.
- Guan, Z., Peng, X., & Fang, J. (2004). Sleep deprivation impairs spatial memory and decreases extracellular signal-regulated kinase phosphorylation in the hippocampus. *Brain Research*, 1018(1), 38–47. <http://dx.doi.org/10.1016/j.brainres.2004.05.032>.
- Guney, E., Fatih Ceylan, M., Tektas, A., Alisik, M., Ergin, M., Goker, Z., & Erel, O. (2014). Oxidative stress in children and adolescents with anxiety disorders. *Journal of Affective Disorders*, 156, 62–66. <http://dx.doi.org/10.1016/j.jad.2013.11.016>.
- Hagewoud, R., Havekes, R., Novati, A., Keijser, J. N., Van der Zee, E. A., & Meerlo, P. (2010). Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. *Journal of Sleep Research*, 19(2), 280–288. <http://dx.doi.org/10.1111/j.1365-2869.2009.00799.x>.
- Halliwell, B. (2007). Biochemistry of oxidative stress. *Biochemical Society Transactions*, 35(Pt 5), 1147–1150. <http://dx.doi.org/10.1042/BST0351147>.
- Harrison, Y., & Horne, J. A. (2000). Sleep loss and temporal memory. *Quarterly Journal of Experimental Psychology A*, 53(1), 271–279. <http://dx.doi.org/10.1080/713755870>.
- Havekes, R., Vecsey, C. G., & Abel, T. (2012). The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. *Cellular Signaling*, 24(6), 1251–1260.

- Hawkins, S. S., & Takeuchi, D. T. (2016). Social determinants of inadequate sleep in US children and adolescents. *Public Health*, 138, 119–126. <http://dx.doi.org/10.1016/j.puhe.2016.03.036>.
- Hermans, E. J., van Marle, H. J., Ossewaarde, L., Henckens, M. J., Qin, S., van Kesteren, M. T., & Fernandez, G. (2011). Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science*, 334(6059), 1151–1153. <http://dx.doi.org/10.1126/science.1209603>.
- Hernandez, P. J., & Abel, T. (2008). The role of protein synthesis in memory consolidation: Progress amid decades of debate. *Neurobiology of Learning and Memory*, 89(3), 293–311. <http://dx.doi.org/10.1016/j.nlm.2007.09.010>.
- Hirotsu, C., Tufik, S., & Andersen, M. L. (2015). Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. *Sleep Science*, 8(3), 143–152. <http://dx.doi.org/10.1016/j.slsci.2015.09.002>.
- Hodge, D., Carollo, T. M., Lewin, M., Hoffman, C. D., & Sweeney, D. P. (2014). Sleep patterns in children with and without autism spectrum disorders: Developmental comparisons. *Research in Developmental Disabilities*, 35(7), 1631–1638. <http://dx.doi.org/10.1016/j.ridd.2014.03.037>.
- Honda, K., Komoda, Y., & Inoue, S. (1994). Oxidized glutathione regulates physiological sleep in unrestrained rats. *Brain Research*, 636(2), 253–258.
- Hong, S., Mills, P. J., Lored, J. S., Adler, K. A., & Dimsdale, J. E. (2005). The association between interleukin-6, sleep, and demographic characteristics. *Brain, Behavior, and Immunity*, 19(2), 165–172. <http://dx.doi.org/10.1016/j.bbi.2004.07.008>.
- Hoshino, Y., & Mishima, M. (2008). Redox-based therapeutics for lung diseases. *Antioxidants and Redox Signaling*, 10(4), 701–704. <http://dx.doi.org/10.1089/ars.2007.1961>.
- Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Research*, 163(2), 195–205.
- Huttenlocher, P. R. (1984). Synapse elimination and plasticity in developing human cerebral cortex. *American Journal of Mental Deficiency*, 88(5), 488–496.
- Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology*, 387(2), 167–178.
- Huttenlocher, P. R., de Courten, C., Garey, L. J., & Van der Loos, H. (1982). Synaptogenesis in human visual cortex—evidence for synapse elimination during normal development. *Neuroscience Letters*, 33(3), 247–252.
- Ikeda, M., Ikeda-Sagara, M., Okada, T., Clement, P., Urade, Y., Nagai, T., & Inoue, S. (2005). Brain oxidation is an initial process in sleep induction. *Neuroscience*, 130(4), 1029–1040. <http://dx.doi.org/10.1016/j.neuroscience.2004.09.057>.
- Irwin, M. R., Wang, M., Ribeiro, D., Cho, H. J., Olmstead, R., Breen, E. C., & Cole, S. (2008). Sleep loss activates cellular inflammatory signaling. *Biological Psychiatry*, 64(6), 538–540.
- Irwin, M. R., Witarama, T., Caudill, M., Olmstead, R., & Breen, E. C. (2015). Sleep loss activates cellular inflammation and signal transducer and activator of transcription (STAT) family proteins in humans. *Brain, Behaviour, and Immunity*, 47, 86–92.
- Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., & Killgore, W. D. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Medicine*, 8(3), 215–221. <http://dx.doi.org/10.1016/j.sleep.2006.08.007>.
- Kalia, M. (2006). Neurobiology of sleep. *Metabolism*, 55(10 Suppl. 2), S2–S6. <http://dx.doi.org/10.1016/j.metabol.2006.07.005>.
- Kametani, H., & Kawamura, H. (1990). Alterations in acetylcholine release in the rat hippocampus during sleep-wakefulness detected by intracerebral dialysis. *Life Sciences*, 47(5), 421–426.
- Kleinova, M., Hewitt, M., Brezova, V., Madden, J. C., Cronin, M. T., & Valko, M. (2007). Antioxidant properties of carotenoids: QSAR prediction of their redox potentials. *General Physiology and Biophysics*, 26(2), 97–103.

- Knutson, K. L., Spiegel, K., Penev, P., & Van Cauter, E. (2007). The metabolic consequences of sleep deprivation. *Sleep Medicine Reviews*, 11(3), 163–178. <http://dx.doi.org/10.1016/j.smrv.2007.01.002>.
- Kopp, C., Longordo, F., Nicholson, J. R., & Luthi, A. (2006). Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. *Journal of Neuroscience*, 26(48), 12456–12465. <http://dx.doi.org/10.1523/JNEUROSCI.2702-06.2006>.
- Krueger, J. M., Frank, M. G., Wisor, J. P., & Roy, S. (2016). Sleep function: Toward elucidating an enigma. *Sleep Medicine Reviews*, 28, 46–54. <http://dx.doi.org/10.1016/j.smrv.2015.08.005>.
- Krueger, J. M., & Obal, F., Jr. (2003). Sleep function. *Frontiers in Bioscience*, 8, d511–519.
- Kurth, S., Achermann, P., Rusterholz, T., & Lebourgeois, M. K. (2013). Development of brain EEG connectivity across early childhood: Does sleep play a role? *Brain Sciences*, 3(4), 1445–1460. <http://dx.doi.org/10.3390/brainsci3041445>.
- Kurth, S., Jenni, O. G., Riedner, B. A., Tononi, G., Carskadon, M. A., & Huber, R. (2010). Characteristics of sleep slow waves in children and adolescents. *Sleep*, 33(4), 475–480.
- Kurth, S., Olini, N., Huber, R., & LeBourgeois, M. (2015). Sleep and early cortical development. *Current Sleep Medicine Reports*, 1(1), 64–73. <http://dx.doi.org/10.1007/s40675-014-0002-8>.
- Kurth, S., Ringli, M., Geiger, A., LeBourgeois, M., Jenni, O. G., & Huber, R. (2010). Mapping of cortical activity in the first two decades of life: A high-density sleep electroencephalogram study. *Journal of Neuroscience*, 30(40), 13211–13219. <http://dx.doi.org/10.1523/JNEUROSCI.2532-10.2010>.
- Kuwano, Y., & Gorospe, M. (2008). Protecting the stress response, guarding the MKP-1 mRNA. *Cell Cycle*, 7(17), 2640–2642. <http://dx.doi.org/10.4161/cc.7.17.6534>.
- van Leeuwen, W. M., Lehto, M., Karisola, P., Lindholm, H., Luukkonen, R., Sallinen, M., & Alenius, H. (2009). Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PLoS One*, 4(2), e4589.
- Lopez, J., Hoffmann, R., & Armitage, R. (2010). Reduced sleep spindle activity in early-onset and elevated risk for depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(9), 934–943. <http://dx.doi.org/10.1016/j.jaac.2010.05.014>.
- Lopez, J., Roffwarg, H. P., Dreher, A., Bissette, G., Karolewicz, B., & Shaffery, J. P. (2008). Rapid eye movement sleep deprivation decreases long-term potentiation stability and affects some glutamatergic signaling proteins during hippocampal development. *Neuroscience*, 153(1), 44–53. <http://dx.doi.org/10.1016/j.neuroscience.2008.01.072>.
- Louis, J., Cannard, C., Bastuji, H., & Challamel, M. J. (1997). Sleep ontogenesis revisited: A longitudinal 24-hour home polygraphic study on 15 normal infants during the first two years of life. *Sleep*, 20(5), 323–333.
- Luna, B., & Sweeney, J. A. (2004). The emergence of collaborative brain function: FMRI studies of the development of response inhibition. *Annals of the New York Academy of Sciences*, 1021, 296–309. <http://dx.doi.org/10.1196/annals.1308.035>.
- MacNee, W. (2001). Oxidative stress and lung inflammation in airways disease. *European Journal of Pharmacology*, 429(1–3), 195–207.
- Mallick, B. N., & Singh, A. (2011). REM sleep loss increases brain excitability: Role of noradrenaline and its mechanism of action. *Sleep Medicine Reviews*, 15(3), 165–178. <http://dx.doi.org/10.1016/j.smrv.2010.11.001>.
- Maret, S., Faraguna, U., Nelson, A. B., Cirelli, C., & Tononi, G. (2011). Sleep and waking modulate spine turnover in the adolescent mouse cortex. *Nature Neuroscience*, 14(11), 1418–1420. <http://dx.doi.org/10.1038/nn.2934>.
- van Marle, H. J., Hermans, E. J., Qin, S., & Fernandez, G. (2009). From specificity to sensitivity: How acute stress affects amygdala processing of biologically salient stimuli. *Biological Psychiatry*, 66(7), 649–655. <http://dx.doi.org/10.1016/j.biopsych.2009.05.014>.

- Masella, R., Di Benedetto, R., Vari, R., Filesi, C., & Giovannini, C. (2005). Novel mechanisms of natural antioxidant compounds in biological systems: Involvement of glutathione and glutathione-related enzymes. *The Journal of Nutritional Biochemistry*, 16(10), 577–586. <http://dx.doi.org/10.1016/j.jnutbio.2005.05.013>.
- Maski, K. P., & Kothare, S. V. (2013). Sleep deprivation and neurobehavioral functioning in children. *International Journal of Psychophysiology*, 89(2), 259–264. <http://dx.doi.org/10.1016/j.ijpsycho.2013.06.019>.
- McDonald, J. W., Johnston, M. V., & Young, A. B. (1990). Differential ontogenic development of three receptors comprising the NMDA receptor/channel complex in the rat hippocampus. *Experimental Neurology*, 110(3), 237–247.
- McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: Allostatics and allostatic load. *Metabolism*, 55(10 Suppl. 2), S20–S23. <http://dx.doi.org/10.1016/j.metabol.2006.07.008>.
- McEwen, B. S., & Karatsoreos, I. N. (2015). Sleep deprivation and circadian disruption: Stress, allostasis, and allostatic load. *Sleep Medicine Clinics*, 10(1), 1–10. <http://dx.doi.org/10.1016/j.jsmc.2014.11.007>.
- McEwen, B. S., & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine*, 153(18), 2093–2101.
- McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, 43(1), 2–15.
- Meerlo, P., Havekes, R., & Steiger, A. (2015). Chronically restricted or disrupted sleep as a causal factor in the development of depression. *Current Topics in Behavioral Neurosciences*, 25, 459–481. http://dx.doi.org/10.1007/7854_2015_367.
- Meerlo, P., Sgoifo, A., & Suchecki, D. (2008). Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Medicine Reviews*, 12(3), 197–210. <http://dx.doi.org/10.1016/j.smrv.2007.07.007>.
- Melgarejo-Gutierrez, M., Acosta-Pena, E., Venebra-Munoz, A., Escobar, C., Santiago-Garcia, J., & Garcia-Garcia, F. (2013). Sleep deprivation reduces neuroglobin immunoreactivity in the rat brain. *NeuroReport*, 24(3), 120–125. <http://dx.doi.org/10.1097/WNR.0b013e32835d4b74>.
- Nahirnyj, A., Livne-Bar, I., Guo, X., & Sivak, J. M. (2013). ROS detoxification and proinflammatory cytokines are linked by p38 MAPK signaling in a model of mature astrocyte activation. *PLoS One*, 8(12), e83049. <http://dx.doi.org/10.1371/journal.pone.0083049>.
- Ng, F., Berk, M., Dean, O., & Bush, A. I. (2008). Oxidative stress in psychiatric disorders: Evidence base and therapeutic implications. *The International Journal of Neuropsychopharmacology*, 11(6), 851–876. <http://dx.doi.org/10.1017/S1461145707008401>.
- Nutt, D., Wilson, S., & Paterson, L. (2008). Sleep disorders as core symptoms of depression. *Dialogues in Clinical Neuroscience*, 10(3), 329–336.
- Orzel-Gryglewska, J. (2010). Consequences of sleep deprivation. *International Journal of Occupational Medicine & Environmental Health*, 23(1), 95–114. <http://dx.doi.org/10.2478/v10001-010-0004-9>.
- Ouyang, M., Hellman, K., Abel, T., & Thomas, S. A. (2004). Adrenergic signaling plays a critical role in the maintenance of waking and in the regulation of REM sleep. *Journal of Neurophysiology*, 92(4), 2071–2082. <http://dx.doi.org/10.1152/jn.00226.2004>.
- Pace-Schott, E. F., Germain, A., & Milad, M. R. (2015). Effects of sleep on memory for conditioned fear and fear extinction. *Psychological Bulletin*, 141(4), 835–857. <http://dx.doi.org/10.1037/bul0000014>.
- Pacher, P., Beckman, J. S., & Liaudet, L. (2007). Nitric oxide and peroxynitrite in health and disease. *Physiological Reviews*, 87(1), 315–424. <http://dx.doi.org/10.1152/physrev.00029.2006>.

- Palagini, L., Baglioni, C., Ciapparelli, A., Gemignani, A., & Riemann, D. (2013). REM sleep dysregulation in depression: State of the art. *Sleep Medicine Reviews*, 17(5), 377–390. <http://dx.doi.org/10.1016/j.smrv.2012.11.001>.
- Paruthi, S., Brooks, L. J., D'Ambrosio, C., Hall, W. A., Kotagal, S., Lloyd, R. M., & Wise, M. S. (2016). Recommended amount of sleep for pediatric populations: A consensus statement of the American Academy of sleep medicine. *Journal of Clinical Sleep Medicine*, 12(6), 785–786. <http://dx.doi.org/10.5664/jcsnm.5866>.
- Patki, G., Solanki, N., Atrooz, F., Allam, F., & Salim, S. (2013). Depression, anxiety-like behavior and memory impairment are associated with increased oxidative stress and inflammation in a rat model of social stress. *Brain Research*, 1539, 73–86. <http://dx.doi.org/10.1016/j.brainres.2013.09.033>.
- Pham-Huy, L. A., He, H., & Pham-Huy, C. (2008). Free radicals, antioxidants in disease and health. *International Journal of Biomedical Sciences*, 4(2), 89–96.
- Pires, G. N., Alvarenga, T. A., Maia, L. O., Mazaro-Costa, R., Tufik, S., & Andersen, M. L. (2012). Inhibition of self-grooming induced by sleep restriction in dam rats. *Indian Journal of Medical Research*, 136(6), 1025–1030.
- Pires, G. N., Bezerra, A. G., Tufik, S., & Andersen, M. L. (2016). Effects of experimental sleep deprivation on anxiety-like behavior in animal research: Systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, 68, 575–589. <http://dx.doi.org/10.1016/j.neubiorev.2016.06.028>.
- Pires, G. N., Tufik, S., & Andersen, M. L. (2013). Grooming analysis algorithm: Use in the relationship between sleep deprivation and anxiety-like behavior. *Progress In Neuro-Psychopharmacology & Biological Psychiatry*, 41, 6–10. <http://dx.doi.org/10.1016/j.pnpbp.2012.11.006>.
- Prabhakar, O. (2013). Cerebroprotective effect of resveratrol through antioxidant and anti-inflammatory effects in diabetic rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 386(8), 705–710. <http://dx.doi.org/10.1007/s00210-013-0871-2>.
- Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S., et al. (2014). Oxidative stress, prooxidants, and antioxidants: The interplay. *BioMed Research International*, 2014, 761264. <http://dx.doi.org/10.1155/2014/761264>.
- Ramanathan, L., Gulyani, S., Nienhuis, R., & Siegel, J. M. (2002). Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. *NeuroReport*, 13(11), 1387–1390.
- Ramanathan, L., Hu, S., Frautschy, S. A., & Siegel, J. M. (2010). Short-term total sleep deprivation in the rat increases antioxidant responses in multiple brain regions without impairing spontaneous alternation behavior. *Behavioural Brain Research*, 207(2), 305–309. <http://dx.doi.org/10.1016/j.bbr.2009.10.014>.
- Ramsawh, H. J., Stein, M. B., Belik, S. L., Jacobi, F., & Sareen, J. (2009). Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *Journal of Psychiatric Research*, 43(10), 926–933. <http://dx.doi.org/10.1016/j.jpsychires.2009.01.009>.
- Ravassard, P., Pachoud, B., Comte, J. C., Mejia-Perez, C., Scote-Blachon, C., Gay, N., et al. (2009). Paradoxical (REM) sleep deprivation causes a large and rapidly reversible decrease in long-term potentiation, synaptic transmission, glutamate receptor protein levels, and ERK/MAPK activation in the dorsal hippocampus. *Sleep*, 32(2), 227–240.
- Reczek, C. R., & Chandel, N. S. (2015). ROS-dependent signal transduction. *Current Opinion in Cell Biology*, 33, 8–13. <http://dx.doi.org/10.1016/j.ceb.2014.09.010>.
- Reimund, E. (1994). The free radical flux theory of sleep. *Medical Hypotheses*, 43(4), 231–233.
- Ringli, M., & Huber, R. (2011). Developmental aspects of sleep slow waves: Linking sleep, brain maturation and behavior. *Progress in Brain Research*, 193, 63–82. <http://dx.doi.org/10.1016/B978-0-444-53839-0.00005-3>.

- Roberts, R. E., & Duong, H. T. (2014). The prospective association between sleep deprivation and depression among adolescents. *Sleep*, 37(2), 239–244. <http://dx.doi.org/10.5665/sleep.3388>.
- Schieber, M., & Chandel, N. S. (2014). ROS function in redox signaling and oxidative stress. *Current Biology*, 24(10), R453–R462. <http://dx.doi.org/10.1016/j.cub.2014.03.034>.
- Seiple, B. D., Blomgren, K., Gimlin, K., Ferrero, D. M., & Noble-Haesslein, L. J. (2013). Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. *Progress in Neurobiology*, 106–107, 1–16. <http://dx.doi.org/10.1016/j.pneurobio.2013.04.001>.
- Serrano, F., & Klann, E. (2004). Reactive oxygen species and synaptic plasticity in the aging hippocampus. *Ageing Research Reviews*, 3(4), 431–443. <http://dx.doi.org/10.1016/j.arr.2004.05.002>.
- Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., et al. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience*, 28(14), 3586–3594. <http://dx.doi.org/10.1523/JNEUROSCI.5309-07.2008>.
- Smith, C. J., Wilkins, K. B., Mogavero, J. N., & Veenema, A. H. (2015). Social novelty investigation in the juvenile rat: Modulation by the mu-opioid system. *Journal of Neuroendocrinology*, 27(10), 752–764. <http://dx.doi.org/10.1111/jne.12301>.
- Solanki, N., Atrooz, F., Asghar, S., & Salim, S. J. N. I. (2016). Tempol protects sleep-deprivation induced behavioral deficits in aggressive male Long–Evans rats. 612, 245–250.
- Son, Y., Cheong, Y. K., Kim, N. H., Chung, H. T., Kang, D. G., & Pae, H. O. (2011). Mitogen-activated protein kinases and reactive oxygen species: How can ROS activate MAPK pathways? *Journal of Signal Transduction*, 2011, 792639. <http://dx.doi.org/10.1155/2011/792639>.
- Spilsbury, J. C., Babineau, D. C., Frame, J., Juhas, K., & Rork, K. (2014). Association between children's exposure to a violent event and objectively and subjectively measured sleep characteristics: A pilot longitudinal study. *Journal of Sleep Research*, 23(5), 585–594. <http://dx.doi.org/10.1111/jsr.12162>.
- Stefanescu, C., & Ciobica, A. (2012). The relevance of oxidative stress status in first episode and recurrent depression. *Journal of Affective Disorders*, 143(1–3), 34–38. <http://dx.doi.org/10.1016/j.jad.2012.05.022>.
- Stenberg, D., & Porkka-Heiskanen, T. (1990). Regulation of sleep. *Duodecim*, 106(22), 1608–1615.
- Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, 262(5134), 679–685.
- Sweatt, J. D., & Hawkins, K. E. (2016). The molecular neurobiology of the sleep-deprived, fuzzy brain. *Science Signaling*, 9(425), fs7. <http://dx.doi.org/10.1126/scisignal.aaf6196>.
- Tancredi, V., D'Antuono, M., Cafè, C., Giovedi, S., Buè, M. C., D'Arcangelo, G., & Benfenati, F. J. (2000). The inhibitory effects of interleukin-6 on synaptic plasticity in the rat hippocampus are associated with an inhibition of mitogen-activated protein kinase ERK. *Journal of Neurochemistry*, 75(2), 634–643.
- Tarokh, L., Carskadon, M. A., & Achermann, P. (2010). Developmental changes in brain connectivity assessed using the sleep EEG. *Neuroscience*, 171(2), 622–634. <http://dx.doi.org/10.1016/j.neuroscience.2010.08.071>.
- Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, 81(1), 12–34. <http://dx.doi.org/10.1016/j.neuron.2013.12.025>.
- Toth, I., & Neumann, I. D. (2013). Animal models of social avoidance and social fear. *Cell and Tissue Research*, 354(1), 107–118. <http://dx.doi.org/10.1007/s00441-013-1636-4>.
- Touchette, E., Cote, S. M., Petit, D., Liu, X., Boivin, M., Falissard, B., & Montplaisir, J. Y. (2009). Short nighttime sleep-duration and hyperactivity trajectories in early childhood. *Pediatrics*, 124(5), e985–993. <http://dx.doi.org/10.1542/peds.2008-2005>.

- Touchette, E., Petit, D., Tremblay, R. E., Boivin, M., Falissard, B., Genolini, C., et al. (2008). Associations between sleep duration patterns and overweight/obesity at age 6. *Sleep*, 31(11), 1507–1514.
- Tsuno, N., Besset, A., & Ritchie, K. (2005). Sleep and depression. *Journal of Clinical Psychiatry*, 66(10), 1254–1269.
- Tudor, J. C., Davis, E. J., Peixoto, L., Wimmer, M. E., van Tilborg, E., Park, A. J., & Abel, T. (2016). Sleep deprivation impairs memory by attenuating mTORC1-dependent protein synthesis. *Science Signaling*, 9(425), ra41. <http://dx.doi.org/10.1126/scisignal.aad4949>.
- Valjent, E., Caboche, J., & Vanhoutte, P. (2001). Mitogen-activated protein kinase/extracellular signal-regulated kinase induced gene regulation in brain: A molecular substrate for learning and memory? *Molecular Neurobiology*, 23(2–3), 83–99. <http://dx.doi.org/10.1385/MN:23:2-3:083>.
- Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell Biology*, 39(1), 44–84. <http://dx.doi.org/10.1016/j.biocel.2006.07.001>.
- Villafuerte, G., Miguel-Puga, A., Rodriguez, E. M., Machado, S., Manjarrez, E., & Arias-Carrion, O. (2015). Sleep deprivation and oxidative stress in animal models: A systematic review. *Oxidative Medicine and Cellular Longevity*, 2015, 234952. <http://dx.doi.org/10.1155/2015/234952>.
- Vollert, C., Zagaar, M., Hovatta, I., Taneja, M., Vu, A., Dao, A., et al. (2011). Exercise prevents sleep deprivation-associated anxiety-like behavior in rats: Potential role of oxidative stress mechanisms. *Behavioural Brain Research*, 224(2), 233–240. <http://dx.doi.org/10.1016/j.bbr.2011.05.010>.
- Wang, D., Malo, D., & Hekimi, S. (2010). Elevated mitochondrial reactive oxygen species generation affects the immune response via hypoxia-inducible factor-1 alpha in long-lived Mcl1+/- mouse mutants. *The Journal of Immunology*, 184(2), 582–590. <http://dx.doi.org/10.4049/jimmunol.0902352>.
- Wang, X., & Michaelis, E. K. (2010). Selective neuronal vulnerability to oxidative stress in the brain. *Frontiers in Aging Neuroscience*, 2, 12. <http://dx.doi.org/10.3389/fnagi.2010.00012>.
- Wheaton, A. G., Chapman, D. P., & Croft, J. B. (2016). School start times, sleep, behavioral, health, and academic outcomes: A review of the literature. *Journal of School Health*, 86(5), 363–381. <http://dx.doi.org/10.1111/josh.12388>.
- Wright, K. P., Jr., Drake, A. L., Frey, D. J., Fleshner, M., Desouza, C. A., Gronfier, C., et al. (2015). Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. 47, 24–34.
- Wulff, K., Gatti, S., Wettstein, J. G., & Foster, R. G. (2010). Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nature Reviews Neuroscience*, 11(8), 589–599. <http://dx.doi.org/10.1038/nrn2868>.
- Yilmaz, E., Sedky, K., & Bennett, D. S. (2013). The relationship between depressive symptoms and obstructive sleep apnea in pediatric populations: A meta-analysis. *Journal of Clinical Sleep Medicine*, 9(11), 1213–1220. <http://dx.doi.org/10.5664/jcsm.3178>.
- Zhang, Z. W. (2006). Canadian association of neurosciences review: Postnatal development of the mammalian neocortex: Role of activity revisited. *The Canadian Journal of Neurological Sciences*, 33(2), 158–169.
- Zhong, J., Carrozza, D. P., Williams, K., Pritchett, D. B., & Molinoff, P. B. (1995). Expression of mRNAs encoding subunits of the NMDA receptor in developing rat brain. *Journal of Neurochemistry*, 64(2), 531–539.